PATENT COOPERATION TREATY

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PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
100843-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE2003/001465	18.09.2003	20.09.2002
International Patent Classification (IPC) or national classification and IPC		
C07C 201/00, C07C 309/63, A61K 31/216, A61P 29/00, C07C 211/55 //C07C 67/03, C07C 303/28		
Applicant		
Nicox SA. et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.03.2004	07.01.2005
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 667 72 88	Authorized officer Per Renström/BS Telephone No. +46 8 782 25 00

Form PCT/IPEA/409 (cover sheet) (January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2003/001465

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))
☐ publication of the international application (under Rule 12.4)
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2003/001465

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-38	YES
	Claims	-	NO
Inventive step (IS)	Claims	-	YES
	Claims	1-38	NO
Industrial applicability (IA)	Claims	1-38	YES
	Claims	-	NO

2. Citations and explanations (Rule 70.7)

Relevant documents (from the International Search Report):

D1: WO9530641 A1
D2: WO9509831 A1
D3: Cainelli et al; Tetrahedron Lett. 28 (1985), 3369-3372.
D4: Cainelli et al; Tetrahedron Lett. 41 (1985), 1385-1392.
D5: Cainelli et al; J. Chem. Soc. Perkin Trans. in (1987), 2637-2642.
D6: Kawamura et al; Chem. Pharm. Bull. 38 (1990), 2092-2096.
D7: Hwu et al; Synthesis (1994), 471-474.
D8: ES2073995 A1

The invention according to claims 1-26 and 33 is directed to a process for the manufacturing of NO-donating pharmaceuticals in the form of nitrooxy-substituted esters. The process comprises (1) an esterification reaction between a pharmaceutically active compound with a carboxylic acid moiety and a diol to form a hydroxy-substituted ester, (2) sulfonation of the hydroxy ester with a sulfonyl chloride to form a sulfonyl-substituted ester and (3) substitution with a nitrate to form the NO-donating nitrooxy-substituted ester.

Claim 2 specifies the active compound to be an NSAID or a COX 1 or COX 2 inhibitor, claims 3-5 contain various structural specifications and claim 6 specifies the active compound to be Diclofenac or Ketoprofen. Claims 7-22 and 33 contain various specifications regarding crystallisation of the product, reagents, solvents, catalysts, nitrate sources, reaction conditions and manufacturing scale. Claim 23 specifies the active compound to be Diclofenac, claim 24 concerns the chemical purity of the product and claims 25-26 specifies the active compound to be Ketoprofen.

.../...

Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment* on _____

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box No. V.

The invention according to claims 32 and 34-35 is directed to sulfonyl intermediates in the process; claims 32 and 35 specifies these to be sulfonyl-substituted esters of Diclofenac and Ketoprofen.

D1 (page 36, line 4 - page 38; example 1, pages 40-51; page 47, line 16 - page 49, line 6; claims) describes the manufacturing of NO-donating compounds, e.g. nitrooxy-substituted esters of Diclofenac and Ketoprofen. The process in D1 comprises (1) production of the acid chloride from the carboxylic acid, (2) reaction of the acid chloride with a halogen-substituted alcohol to form a halogen-substituted ester and (3) substitution with $AgNO_3$ in acetonitrile to form the nitrooxy-substituted ester.

See also D2 (example 1, pages 14-16; the claims), disclosing the manufacturing of NO-donating compounds, e.g. nitrooxy-substituted esters of Naproxen.

D1 is considered to represent the closest prior art. The main difference between D1 and the present invention is to use sulfonate instead of halide as a leaving group in the nitrate substitution, and to use tetraalkylammonium nitrate or another metal nitrate than silver nitrate. This solves a number of problems, such as expensive reagents ($AgNO_3$), troublesome work-up and an unpure product.

D3-D8 disclose the manufacturing of nitrooxy-substituted compounds through nitrate substitution of sulfonates, analogously with step 3 in the process of the present invention. The sulfonates are made from the corresponding hydroxy compounds and sulfonyl chlorides, analogously with step 2 in the present invention.

The following reagents and solvents are used in D3-D8:

D3 and D4: tosylate and tetrabutylammonium nitrate in pentane, toluene or benzene (corresponding to step 3); p-TsCl in CH_2Cl_2 in the presence of triethylamine and DMAP (corresponding to step 2).

D5: mesylate and NBu_4NO_3 in toluene (step 3); MsCl in CH_2Cl_2 in the presence of triethylamine (step 2).

.../...

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Previous Supplemental Box.

D6: benzenesulfonate and NBu_4NO_3 in toluene (step 3); pyridine (step 2).

D7: tosylate, $NaNO_3$ and a catalytic amount of NBu_4NO_3 in benzene and water (step 3).

D8: alkyl or aryl sulfonate (e.g. tosylate) and a metal nitrate (e.g. $NaNO_3$) in DMF, dimethylacetamide (DMA), acetonitrile and DMSO, all being polar, aprotic solvents (step 3); TsCl in piperidine (step 2).

D3-D8 disclose reactions analogous with step 2 and 3 in the present invention, with the difference that unreacting parts of the molecule have a different structure. The invention according to claim 11 additionally differs in that the solvent in step 2 is not CH_2Cl_2, pyridine or piperidine. The invention according to claim 16 differs in that the nitrate source is a salt with a metal of Group I or II (which however does not exclude the presence of a tetraalkylammonium nitrate as a phase transfer catalyst). The invention according to claim 21 differs from D3-D7 but not from D8 in that the solvent is polar and aprotic instead of unpolar and aprotic.

In attempting to solve the problem of finding a better way of manufacturing the NO-donating nitrooxy-substituted esters in D1, the person skilled in the art would get the idea from D3, D4, D5 or D6 to use a tetraalkylammonium nitrate instead of $AgNO_3$, and to use a sulfonyl-substituted ester instead of a halogen-substituted ester as an intermediate. Likewise, he would get the idea from D7 or D8 to use an alkalimetal nitrate and a sulfonyl-substituted ester.

It is furthermore obvious to the person skilled in the art to use a hydroxy-substituted ester as a starting material for the synthesis of the sulfonyl-substituted ester, and it is also obvious that the firsthand choice for the synthesis of the hydroxy-substituted ester would be the reaction between a suitable diol and either the parent carboxylic acid compound or the corresponding acid chloride.

For these reasons the invention according to present claims 1-26 and 32-35 is considered to lack an inventive step in view of D1 in combination with any of the documents D3-D8.

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Previous Supplemental Box.

It is however recognised that the specific combinations of reagents, solvents and reaction conditions that have been developed in the present invention for the manufacturing of those specific types of products for which support is disclosed, namely the products in claims 5, 6, 23, 25 and 26, is not obvious to the person skilled in the art. Therefore, a combination of any of claims 5, 6, 23, 25 and 26 with claims 3, 4, 9, 10, 11 and 18 may be considered to involve an inventive step.

The invention according to claims 27-31 and 36-38 is directed to the 2-[2-(nitrooxy)ethoxy]-ethyl ester of Diclofenac in crystalline form. This compound is known from D1 in an unspecified form. Since the mere crystallisation of a known compound is considered to constitute common practise, and since nothing unexpected or inventive could be identified in the crystallisation process as described in present claims 7-8, the invention according to claims 27-31 and 36-38 is considered to lack an inventive step in view of D1 and known art of crystallisation.

In summary, the invention according to present claims 1-38 is novel and industrially applicable but is considered to lack an inventive step.